REMARKS

Reconsideration of the application in view of the above amendments and following remarks is respectfully requested.

The electronic and paper copies of the Sequence Listing supplied herewith are provided to correct simple oversights in the original Sequence Listing. Sequence identifier number 48 has been added to the enclosed Sequence Listing. This sequence was disclosed in the application as originally filed, but not included in the original Sequence Listing. The sequence was originally disclosed in Figure 2 and at page 30, line 15. No new matter was added.

Claims 18-22, 24-32, 37-39 and 65 are currently pending and under consideration. Claims 18, 24 and 27 have been amended. Claims 25, 38, 39 and 65 have been canceled. New claim 66 has been added, directed to a fusion protein having a single-chain Fv derived from variable light and variable heavy chains of B9E9 specifically identified in SEQ ID NO:8. The amended claims have been amended for clarification purposes and to advance one aspect of the invention solely for the purpose of expediting allowance. Support for the amendments can be found throughout the specification and at specific sections as noted in the following remarks. The amendments are made without prejudice to filing a continuation, continuation-in-part, or divisional thereon. No new matter has been added.

Objection to Previous Amendment

The amendment filed February 7, 2002, stands objected to under 35 U.S.C. § 132 because it is alleged to introduce new matter into the disclosure.

An amendment was made to the description to respond to this objection. The added material identified by the Examiner as new matter was deleted, thereby rendering this objection moot.

Objections to Specification

The disclosure stands objected to because it refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified.

An amendment was made to the description to respond to this objection. Reference to the hyperlink was deleted.

The disclosure further stands objected to because sequence disclosures encompassed by definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2) are not properly identified by sequence identifier in accordance with 37 C.F.R. § 1.821(d).

Amendments were made to the description to respond to this objection. These amendments add sequence identifiers as required under 37 C.F.R. § 1.821(d). The amendment to the description regarding Figure 2 also includes additional descriptive language to allow for sensible insertion of sequence identifiers.

The electronic and paper copies of the Sequence Listing included herewith are identical and do not go beyond the disclosure of the application as originally filed. Applicants respectfully submit that the above-identified application and Sequence Listing are now in compliance with 37 C.F.R. §§ 1.821-1.825 and WIPO Standard 25.

The disclosure further stands objected to because the use of improperly demarcated trademarks has been noted.

Amendments were made to the description to respond to these objections. Each trademark identified in the description has been demarcated by capitalization. No new matter has been added.

Accordingly, the relevant portions of the specification have been amended, thereby rendering the present objections moot.

Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 25, 27 and 65 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Action alleges that the claim(s) contain subject matter that was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Action asserts that it is unclear whether a hybridoma cell line that produces an antibody having the exact structural and chemical identity of the antibody B9E9 is know and publicly available, or can be reproducibly isolated without undue experimentation. The Action further asserts that, without access to such cell line, it would not be possible to practice the claimed invention because it would not be possible to make the antibody.

Applicants respectfully disagree. Applicants submit that, since the sequences of the variable light and variable heavy domains of B9E9 are provided, one of skill in the art would be able to synthesize the requisite nucleotide sequences using standard methods. Accordingly, claim 27 has been amended to specifically incorporate the sequence identifiers of the variable light and variable heavy domains of B9E9. Without acquiescing to the grounds for rejection, Applicants have at this time cancelled claims 25 and 65 in order to focus on a particular aspect of the invention solely for the purpose of expediting allowance. Further, Applicants have added new claim 66, which also specifically incorporates the sequence identifier of the variable light and variable heavy domains of B9E9. In view of these remarks and amendments, Applicants submit that access to a hybridoma cell line is not necessary to enable one skilled in the art to make the claimed antibody and corresponding fusion protein. In fact, Applicants submit that such disclosure fully enables the invention as claimed. Applicants thus respectfully request that this grounds for rejection be withdrawn.

Rejection under 35 U.S.C. § 112, Second Paragraph, Indefiniteness

Claims 25, 27 and 65 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

Applicants note that claim 27 has been amended to recite that the antibody binds CD20. Further, as noted above, claim 27 has been amended to incorporate the sequence listing of the variable light and variable heavy domains of B9E9. Applicants again submit that by doing so, the alleged requirement to make available and identify the hybridoma producing this antibody is unnecessary. Claims 25 and 65, as noted above, have been cancelled. Applicants thus respectfully request that these grounds for rejection be withdrawn.

Rejection under 35 U.S.C § 102, Anticipation

Claims 18-22, 24, 26, 28-32, 38, 39 and 65 stand rejected as allegedly being anticipated by U.S. Patent No. 5,571,894 A, as evidenced by Database PIR 78 Accession No. A23513 (03 November 1987), Kumar *et al.* (*Semin. Oncol.* 28:27-32, 2001), and U.S. Patent No. 6,451,995 B1. More particularly, the Action alleges that 5,571,894 A ('894) teaches a fusion protein comprising streptavidin from Streptomyces avidinii, which is capable of strongly binding biotin, and a single-chain antibody (scFv) that binds Her2/neu, and that the fusion protein can be expressed as a soluble protein in the periplasm. Based on the cited evidence, the Examiner has identified streptavidin in 5,571,894 A as a protein having an amino acid sequence of 183 amino acids that is identical to SEQ ID NO:2.

Applicants respectfully traverse this ground for rejection and submit that 5,571,894 A fails to anticipate the instant claims, as amended. Applicants note that claims 38, 39 and 65 have been cancelled. Applicants further note that claims 18 and 24 have been amended to be directed to a particular aspect of the invention, solely for the purpose of expediting allowance. In this regard, the claims as now amended are directed to a recombinant fusion protein comprising amino acids 1 to 159 of full-length genomic streptavidin, corresponding to amino acids 25 to 183 of SEQ ID NO:2, which is nowhere discussed in 5,571,894 A does not anticipate the instant claims, as amended. Thus, Applicants respectfully request that this ground for rejection be withdrawn.

Rejection under 35 U.S.C. § 103(a), Obviousness

Claims 18-22, 24, 26, 28-30, 38, 39 and 65 stand rejected under 35 U.S.C § 103(a) as allegedly unpatentable over Alvarez-Diez *et al.* (*Nucl. Med. Biol.* 23:459-466, 1996) in view of Goshorn *et al.* (*Cancer Research* 53:2123-2127, 1993) and WO 89/03422 A, as evidenced by Guan *et al.* (*Appl. Microbiol. Biotechnol.* 44:753-758, 1996). Specifically, the Action alleges that Alvarez-Diez *et al.* teaches a fusion protein comprising streptavidin chemically conjugated to anti-TAG72 monoclonal antibody CC49. Applicants note that the Examiner acknowledges that Alvarez-Diez *et al.* does not expressly teach a fusion protein

produced by recombinant DNA technology as a soluble protein in the periplasmic space, wherein streptavidin and the antibody are separated by a linker of between 5 and 10 amino acids, nor that it expressly teaches substituting a single-chain Fv antibody fragment derived from monoclonal antibody CC49, comprising a linker of at least 15 amino acids connecting the light and heavy chain variable domains. Rather, the Examiner contends that Goshorn *et al.* teaches a recombinant DNA method for preparing, and a genetic construction encoding, a fusion protein comprising an antibody and an enzyme and further discloses that such fusion protein may have advantages over that produced by chemical conjugation. The Examiner further contends that WO 89/03422 A (Edwards) teaches a synthetic DNA molecule encoding a streptavidin molecule, which comprises an amino acid sequence that is identical to that set forth in SEQ ID NO:2, and further that it discloses that the DNA molecule can be used to produce a genetic construct encoding a fusion protein possessing biotin binding activity. The Examiner further asserts that Guan *et al.* teaches that, when the streptavidin gene from *S. avidinii* was expressed in *E. coli* as a non-fusion protein, the protein accumulated primarily in inclusion bodies, but that a fusion protein comprising streptavidin expressed as soluble protein in E. coli.

Applicants traverse these bases of rejection and submit that the presently claimed invention is not obvious in light of the cited references, either alone or in combination. Applicants note that claims 38, 39 and 65 have been cancelled. Applicants respectfully point out that the Federal Circuit has held that in establishing a prima facie case of obviousness, "obvious to try" is not a legitimate test of patentability. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, 1598 (Fed. Circ. 1988). Applicants submit that, while the ordinary skilled artisan may have been tempted to produce the chemically conjugated fusion protein of Alvarez-Diez *et al.* by recombinant methodologies using single-chain antibodies to study the potential of such fusion protein in imaging or treating tumors, the preparation of constructs of the present invention, which resulted in surprisingly successful production of the recombinant fusion proteins, would not have been at all obvious. Applicants submit that, beginning with the chemical conjugates of Alvarez-Diez *et al.*, implementation of recombinant methodologies resulting in the present invention, including selection of antibody fragment, streptavidin species, and the various linkers, would require an undue degree of experimentation. However, even with undue experimentation,

it is not at all apparent that the skilled artisan would successfully produce the variety of fusion proteins comprising different antibodies as have resulted from the present invention. Applicants submit that WO 89/03422 A does not overcome this defect, as it provides no data or other insight for the identification of successful fusion protein constructs. In fact, it is noted therein that "it is by no means easy to predict the design of an improved streptavidin gene, since the factors that determine the expressibility of a given DNA sequence are still poorly understood." (WO/ 89/03422 A, page 2, second full paragraph) Concerning Guan *et al.*, the Examiner acknowledges that neither Alvarez-Diez *et al.*, nor Goshorn *et al.*, suggests that a fusion protein comprising streptavidin and a single-chain antibody, which is produced by recombinant DNA technology in bacteria, is expressed as soluble protein in the periplasm, the Examiner contends that, in the absence of any evidence to the contrary, the fusion protein of Guan *et al.* is deemed the same as the that of claim 24. As noted above, the fusion protein of claim 24, as amended, expresses at surprisingly high levels in the periplasm. There is no evidence in Guan *et al.*, to suggest levels of expression in excess of those low levels commonly reported in the literature at the time; otherwise it would have been emphasized. Applicants submit that only in hindsight can the surprising success of the present invention appear obvious. In view of these remarks, Applicants request that the Examiner reconsider and withdraw this ground for rejection.

Claims 31, 32 and 65 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Alvarez-Diez *et al.* (*Nucl. Med. Biol.* 23:459-466, 1966) in view of Goshorn *et al.* (*Cancer Research* 53:2123-2127, 1993) and WO 89/03422 A, as evidenced by Guan *et al.* (*Appl. Microbiol. Biotechnol.* 44:753-758, 1996), in further view of Desplancq *et al.* (*Protein Engineering* 7:1027-1033, 1994). Specifically, the Action alleges the teachings of Alvarez-Diez *et al.*, Goshorn *et al.*, and WO 89/03422 A (Edwards), as noted above. Applicants note that the Examiner acknowledges that Alvarez-Diez *et al.* does not expressly teach substituting a single-chain Fv antibody fragment comprising a linker of at least 20 amino acid residues connecting the light and heavy variable chains or comprising a linker of at least four repeats of SEQ ID NO:47, and that Goshorn *et al.* does not expressly teach or suggest a single-chain antibody having such a linker. Rather, the Examiner rather contends that Desplancq *et al.* teaches a single-chain Fv fragment of monoclonal antibody of anti-TAG72 monoclonal antibody B72.3, in which the

variable light and heavy chains are joined by at least 20 amino acids, wherein the linker consists of at least four repeats of SEQ ID NO:47.

Applicants traverse these bases of rejection and submit that the presently claimed invention is not obvious in light of the cited references, either alone or in combination. Applicants note that Claim 65 has been cancelled, not in acquiescence, but solely for purposes of expediting examination. For the reasons described above, Applicants submit that Alvarez-Diez *et al.*, Goshorn *et al.* and WO 89/03422 A (Edwards) have not, either alone or in combination, provided the teaching necessary to achieve the claimed invention. Applicants further submit that Desplancq *et al.* fails to resolve this defect. Thus, Applicant respectfully request that the Examiner reconsider and withdraw this basis of rejection.

Claims 18-21, 24, 26, 28-30, 37 and 65 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Dubel *et al.* (*J. Immunol. Meth.* 178:201-209, 1995) in view of Gallizia *et al.* (*Prot. Expr. Purif.* 14:192-196, 1998), Ohno *et al.* (*DNA and Cell Biol.* 15:401-406, 1996), and McLaughlin *et al.* (*Oncology* 12:1763-1769, 1998), as evidenced by Kipriyanov *et al.* (*Human Antibodies and Hybridomas* 6:93-101, 1995) and Database PIR 78 Accession No. A23513 (03 November 1987). Specifically, the Action alleges that Dubel *et al.* teaches a fusion protein comprising a portion of genomic streptavidin and an antibody or antigen-binding fragment thereof and that the fusion protein of Dubel *et al.* comprises a single-chain Fv antibody fragment in which a linker connects the variable light and variable heavy chains. The Action further alleges that the fusion protein of Dubel *et al.* consists of 126 amino acids of streptavidin.

Applicants respectfully traverse these bases of rejection and submit that the presently claimed invention is not obvious in light of the cited references, either alone or in combination. Applicants note that claim 65 has been cancelled, not in acquiescence, but solely for purposes of expediting examination. Applicants further note that claims 18 and 24 have been amended to be directed to a particular aspect of the invention, solely for the purpose of expediting allowance. In this regard, the claims as now amended are directed to a recombinant fusion protein comprising amino acids 1 to 159 of full-length genomic streptavidin. Applicants submit that, in view of this amendment, Dubel *et al.* (*J. Immunol. Meth.* 178:201-209, 1995), Gallizia *et al.* (*Prot. Expr. Purif.* 14:192-196, 1998), Ohno *et al.* (*DNA and Cell Biol.* 15:401-

406, 1996), and McLaughlin *et al.* (*Oncology* 12:1763-1769, 1998) do not, either alone or in combination, provide the teaching necessary to achieve the claimed invention. Thus, Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

Claims 22 and 65 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Dubel *et al.* (*J. Immunol. Meth.* 178:201-209, 1995) in view of Gallizia *et al.* (*Prot. Expr. Purif.* 14:192-196, 1998), Ohno *et al.* (*DNA and Cell Biol.* 15:401-406, 1996), and McLaughlin *et al.* (*Oncology* 12:1763-1769, 1998), as evidenced by Kipriyanov *et al.* (*Human Antibodies and Hybridomas* 6:93-101, 1995) and Database PIR 78 Accession No. A23513 (03 November 1987), further in view of Goshorn *et al.* (*Canc. Res.* 53:2123-2127, 1993).

Applicants respectfully traverse these bases of rejection and submit that the presently claimed invention is not obvious in light of the cited references, either alone or in combination. Applicants note that claim 65 has been cancelled, not in acquiescence, but solely for purposes of expediting examination. Applicants further note that claim 18, from which claim 22 depends, has been amended to be directed to a particular aspect of the invention, solely for the purpose of expediting allowance. In this regard, the claims as now amended are directed to a recombinant fusion protein comprising amino acids 1 to 159 of full-length genomic streptavidin. Applicants submit that, in view of this amendment, Dubel *et al.* (*J. Immunol. Meth.* 178:201-209, 1995), Gallizia *et al.* (*Prot. Expr. Purif.* 14:192-196, 1998), Ohno *et al.* (*DNA and Cell Biol.* 15:401-406, 1996), and McLaughlin *et al.* (*Oncology* 12:1763-1769, 1998), further in view of Goshorn *et al.* (*Canc. Res.* 53:2123-2127, 1993), do not, either alone or in combination, provide the teaching necessary to achieve the claimed invention. Thus, Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

Claims 31, 32 and 65 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Dubel *et al.* (*J. Immunol. Meth.* 178:201-209, 1995) in view of Gallizia *et al.* (*Prot. Expr. Purif.* 14:192-196, 1998), Ohno *et al.* (*DNA and Cell Biol.* 15:401-406, 1996), and McLaughlin *et al.* (*Oncology* 12:1763-1769, 1998), as evidenced by Kipriyanov *et al.* (*Human Antibodies and Hybridomas* 6:93-101, 1995) and Database PIR 78 Accession No. A23513 (03 November 1987), further in view of Desplancq *et al.* (*Prot. Eng.* 7:1027-1033).

Applicants respectfully traverse these bases of rejection and submit that the presently claimed invention is not obvious in light of the cited references, either alone or in combination. Applicants note that claim 65 has been cancelled, not in acquiescence, but solely for purposes of expediting examination. Applicants further note that claim 18, from which claims 31 and 32 depend, has been amended to be directed to a particular aspect of the invention, solely for the purpose of expediting allowance. In this regard, the claims as now amended are directed to a recombinant fusion protein comprising amino acids 1 to 159 of full-length genomic streptavidin. Applicants submit that, in view of this amendment, Dubel *et al.* (*J. Immunol. Meth.* 178:201-209, 1995), Gallizia *et al.* (*Prot. Expr. Purif.* 14:192-196, 1998), Ohno *et al.* (*DNA and Cell Biol.* 15:401-406, 1996), and McLaughlin *et al.* (*Oncology* 12:1763-1769, 1998), further in view of Desplancq *et al.* (*Prot. Eng.* 7:1027-1033), do not, either alone or in combination, provide the teaching necessary to achieve the claimed invention. Thus, Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

Double Patenting

Claims 18-22, 24, 26, 28-32, 37-39 and 65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-24, 26, 27, 29-38, 40-42 and 79-81 of co-pending Application No. 10/013,173.

With respect to any possible rejections under 35 U.S.C. § 103(a) utilizing the above-identified application, it is hereby submitted that the above-noted inventions were commonly owned at the time the present invention was made under 35 U.S.C. § 103(c).

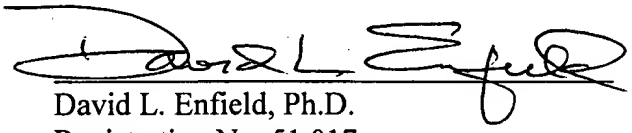
Applicants hereby respectfully request that the above rejections be held in abeyance until allowable subject matter in identified herein.

In light of the amendments and remarks set forth above, Applicants respectfully submit that all the Examiner's rejections have been overcome. Reconsideration of the application and allowance of all pending claims are respectfully requested. If there is any further matter requiring attention prior to allowance of the subject application, the Examiner is respectfully requested to contact the undersigned patent agent (at 206.622.4900) to resolve the matter.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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